REMARKS

Claims 1-114, 125-126, 128-129 and 134-150 have been canceled. Cancellation of these claims should not be construed as an acquiescence to any of the rejections and Applicants reserve the right to pursue these claims in a continuation application(s). Claims 115-124, 127, 130-133 and 151-152 are pending. Claims 115-124, 127, 130, 131 and 133 have been allowed. Claim 132 has been amended to correct an informality. Claims 151 and 152 have been amended to specify a pharmaceutical composition. Support for amended claims 151 and 152 can be found at page 47, line 3 to page 55, line 16.

Claim for Domestic Priority under 35 U.S.C. § 119(e)

Claims 148-150 have been canceled. Thus, priority of these claims is no longer at issue.

Objections to the claims

Claim 132 has been objected to because the molar designation should be in superscript. This objection is obviated by amended claim 132.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 127, 151 and 152 have been rejected under 35 U.S.C. § 112, first paragraph for failure to comply with the written description requirement. The Examiner contends that disclosure of the non-cross reactivity of the 10D1 human monoclonal antibody with non-lymphoid tissue does not provide adequate written description for a subgenus of human anti-CTLA-4 antibodies that do not cross-react with non-lymphoid tissue.

The Examiner does not support the statement that "this description of a single species of 10D1 does not appear to be sufficient to describe the subgenus," except to cite In re Smith for the proposition that "it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads" (Office Action mailed June 14, 2004, page 5).

The court in In re Smith rejected the argument that as a rule disclosure of a genus and a single species provided sufficient written description for a subgenus. In re Smith, 173 USPQ 679, 683 (CCPA 1972) ("From this passage emerges the rule relied upon by appellant to the effect that

the disclosure of a genus and a species of a subgenus is a sufficient description of the subgenus. We do not now feel that such a rule is consonant with either the letter or spirit of the description requirement of § 112.") In re Smith does not preclude that the disclosure of a genus and a single species can provide adequate written description. "Precisely how close the description must come to comply with § 112 must be left to case-by-case development....[I]t cannot be said that such a subgenus is necessarily always implicitly described by a genus encompassing it and a species upon which it reads." *Id.*

Applicant's previous argument does not conflict with this case law because Applicant does not assert a general rule. Rather, Applicant's previous argument pointed out that because the application provides methods that are straight forward and enabled by the specification for (a) producing human sequence antibodies the specifically bind CTLA-4; and (b) screening those antibodies for cross-reactivity with various tissues, the description of the 10D1 antibody, coupled with the other disclosure in this application, is sufficient for one skilled in the art to recognize that Applicants were in possession of the necessary common attributes or features possessed by members of the claimed subgenus (Response to Office Action and Amendment under 37 C.F.R. 1.111, dated November 23, 2003). This is a case where disclosure of a genus and a single species provides adequate written description of the subgenus.

The Federal Circuit has recently reiterated their position that description of a single species is sufficient description of a genus if the species is representative of the genus. The written description requirement can be met "by means of a recitation of a representative number [of species] falling within the scope of the genus *or* of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." University of California v. Eli Lilly and Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997) (emphasis added). Thus, *either* a description of the features common to members of the genus *or* a description of the features of a representative number of species is required to satisfy the written description requirement.

The Federal Circuit does not require a written description of any set minimum number of species, just that the number of species must be representative of the genus. *See id.* Thus, the recitation of even one species, if it is representative of the genus, can satisfy the written description requirement. In Lilly, the Federal Circuit stated that the description of one species could, but did not

necessarily, describe the genus to which it belonged. *Id.* at 1568 ("[D]escription of one species is not necessarily a description of the genus"). It follows that a description of one species is a description of a genus in some cases.

Description of one species is most likely to be representative of the genus to which it belongs when the art is predictable. The Federal Circuit accepted that the antibody art is mature and predictable when it adopted PTO Guidelines, which acknowledged: "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004) (quoting Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1324-1325 (Fed. Cir. 2002)).

Accordingly, description of the 10D1 antibody is sufficient to meet the written description for the genus of monoclonal antibodies or anti-binding portions thereof that specifically bind to human CTLA-4 and do not cross react with non-lymphoid tissue. Thus, this 35 U.S.C. § 112, first paragraph rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 148-150 have been canceled. Thus, this rejection is obviated.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 148-150 have been canceled. Thus, this rejection is obviated.

Rejections under 35 U.S.C. § 102(e)

Claims 148 and 151 have been rejected under 35 U.S.C. § 102(e) as anticipated by Hanson et al., U.S. Patent No. 6,682,736 ("Hanson"). Claim 148 has been canceled. Thus, the 35 U.S.C. § 102(e) rejection of claim 148 is obviated.

According to the Examiner, Hanson discloses antibodies specific to CTLA-4 and, because expression of CTLA-4 is limited to lymphoid tissue, the antibodies of Hanson do not cross-react with non-lymphoid tissue.

The instant specification discloses a representative species of therapeutically effective monoclonal antibodies that was evaluated for cross-reactivity to unintended human tissue targets.

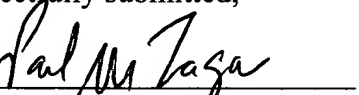
The human tissues evaluated included all those recommended in the 1997 FDA publication "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" ("FDA document") (cited in the specification at page 78, lines 14-15). According to this FDA document, "[w]hen the same or related antigenic determinant is expressed on human cells or tissues other than the intended target tissue, binding of the antibody may have serious consequences, particularly when pharmacologically active antibodies...are used. Accordingly, cross-reactivity studies with human tissues...should always be conducted prior to phase 1 to search for cross-reactions or non-target tissue binding" (FDA document, pages 29-30, copy enclosed). The monoclonal antibody disclosed in the instant specification did not exhibit such unintended cross-reactivity (page 78, lines 6-8) and is, therefore, suitable for use in a pharmaceutical composition. Hanson does not disclose a therapeutically effective anti-CTLA-4 monoclonal antibody that does not bind to an unintended target (i.e., non-lymphoid tissue). Thus, there is no disclosure in Hanson of a therapeutically-effective human monoclonal antibody suitable for use in a pharmaceutical composition. Accordingly the rejection of claim 151 as anticipated by Hanson should be withdrawn.

Conclusion

All of the pending claims in this application are believed to be in condition for allowance. Entry and consideration of these amendments and remarks are therefore respectfully requested.

Respectfully submitted,

Dated: September 14, 2004

By 

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Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 28,1997

Date: February 27, 1997

From: Kathryn C. Zoon , Ph.D., Director
Center for Biologics Evaluation and Research
Food and Drug Administration

Subject: Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use

To: Manufacturers of Biological Products and Other Interested Persons

This Points to Consider (PTC) document has been developed for manufacturers of monoclonal antibody products for human use. These "Points" are not regulations nor are they guidelines, but represent the current thinking that the Center for Biologics Evaluation and Research (CBER) staff believe should be considered at this time. This 1997 PTC document supersedes the 1994 PTC document of the same title, announced in the Federal Register of August 3, 1994 (59 FR 39571).

It is our intention to continuously update and revise this document in order to improve its usefulness. We invite your review and comment on the "Points". Comments should be identified with the docket number 94D-0259. Two copies of any comments should be submitted except that individuals may submit one copy. All comments should be addressed to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

_____-s-_____
Kathryn C. Zoon, Ph.D.

analysis of glycosylation including carbohydrate content and composition, peptide mapping or other appropriate tests. *In vitro* functional comparison should include assays aimed at the characterization of the biological function of the antibody (e.g., binding, cytotoxicity, epitope modulation, etc.). Whenever possible, a comparison of the affinity constants of the two products is highly recommended.

3. Animal studies

Depending on the quality of the data and the type of *in vitro* assays, the nature of the manufacturing change and the types of product differences observed or anticipated, a program of comparative testing (pharmacokinetics, etc.) in appropriate animal models may be considered in lieu of human clinical data when biochemical testing shows differences or cannot exclude significant differences in two products. In some cases, pharmacokinetic studies are complementary to *in vitro* studies. Pharmacokinetic studies in animals may be informative, even in the absence of the target antigen, depending upon the question to be addressed and the expected contribution of antigen binding to the biodistribution of specific mAb in humans. The extent of animal toxicity testing that may be needed to assess comparability will depend upon the safety profile of each specific product, the magnitude of the changes in manufacturing, the presence or absence of detectable differences in purity, structure or *in vitro* activity. Sponsors are encouraged to discuss plans for comparative testing of the two products in animals with CBER or to submit proposal for such testing to CBER for review and comment. The proposed program should be appropriate in view of biochemical data and include statistical considerations.

4. Clinical studies to support manufacturing changes

Comparative clinical evaluation of the products produced by different or scaled-up manufacturing schemes may be needed in certain situations:

a. Product activity cannot be adequately characterized by analytical testing.

b. Biochemical or biological testing show differences in the products.

c. Animal testing reveals significant pharmacokinetic or other differences in the products.

d. The formulation of the product has been changed in a way that can affect its bioavailability. The latter changes generally dictate a need for clinical pharmacokinetic studies.

Pharmacokinetic, safety and/or efficacy data may be required depending upon the nature and magnitude of the observed changes in the biochemical and or biological properties of the product.

Additional information on product comparability testing can be found in ref. 23.

III. PRECLINICAL STUDIES

A. TESTING CROSS-REACTIVITY OF MAB

When the same or related antigenic determinant is expressed on human cells or tissues other than the intended target tissue, binding of the antibody to this tissue may be observed. Non-target tissue binding may have serious consequences, particularly when pharmacologically active antibodies or cytotoxic immunoconjugates are used. Accordingly, cross-reactivity studies with human tissues (or cells if

applicable) should always be conducted prior to phase 1 to search for cross-reactions or non-target tissue binding. In the special case of bispecific antibodies, each parent antibody should be evaluated individually, in addition to testing of the bispecific product.

1. *In vitro* testing for cross-reactivity

Human cells or tissues are presently surveyed immunocytochemically or immunohistochemically. Appropriate newer technologies should be employed as they become available and validated.

a. Reactivity of the antibody or immunoconjugate should be determined with the quick-frozen adult tissues listed in Appendix I. Surgical samples are preferred. Post-mortem samples are acceptable with adequate tissue preservation. Tissues from at least three unrelated human donors should be evaluated in order to screen for polymorphism. The effect of fixatives on tissues that are known to be positive should be evaluated to ensure that the target antigen is preserved during tissue processing.

b. In special situations it may be appropriate to assay cross-reactivity on representative cultured cell lines, stem cells, and embryonic/fetal tissue.

c. Several concentrations of the product should be tested. The ability to detect cross-reactions may depend on antibody concentration. Antibody affinities as well as expected achievable peak plasma concentrations should be considered when choosing the proper concentrations for tissue binding studies. An "ideal" concentration for these studies may be the lowest mAb concentration that produces maximum (plateau) binding to the target antigen. An attempt should also be made to compare the ratio of specific binding to target tissue to specific binding to cross-reactive tissue. Because non-specific as well as Fc-mediated binding may be observed, it should be distinguished from specific cross-reactions using inhibition assays with purified antigen, when available.

d. Positive and negative controls are essential for interpreting study results. Controls confirm the acceptable condition of the tissues and adequacy of the assay. Anti-transferrin receptor mAb may be a useful positive control, since transferrin receptor is a common and abundant molecule on the surface of growing normal and tumor cells.

e. If a conjugated, chemically modified antibody or antibody fragment is to be used clinically, it should be tested in that form if at all feasible. The substitution of antibodies of similar specificity for cross-reactivity testing is discouraged.

f. When cross-reactions are encountered and there is a reason to suspect genetic polymorphism of the target antigen, studies should be expanded to a larger panel of tissues to better characterize this polymorphism.

g. A comparison of *in vitro* cross-reactivity in tissues from different species is important in determining the most relevant animal for subsequent toxicology studies.

2. *In vivo* testing for cross-reactivity

Cross-reactivity of a monoclonal antibody with non-target human tissues should dictate a comprehensive *in vivo* investigation in animals, when appropriate models are available. This finding, particularly with cytolytic immunoconjugates or antibodies with ADCC activity, generally indicates the desirability of more extensive preclinical testing, including studies in more than one animal species over a range of doses and

repeat dose animal studies. Localization to non-target tissues should be kept in mind when designing clinical trials.

B. PRECLINICAL PHARMACOLOGY AND TOXICITY TESTING

1. General considerations

a. Preclinical safety testing of mAb is designed to identify possible toxicities in humans, to estimate the likelihood and severity of potential adverse events in humans, and to identify a safe starting dose and dose escalation, when possible. Preclinical testing concerns surrounding mAb products include their immunogenicity, stability, tissue cross-reactivity, and effector function(s). Species differences may complicate the design and interpretation of preclinical studies. CBER recognizes that animal models expressing the antigen of interest or a closely related, highly cross-reactive epitope are not always available. Pharmacokinetic and pharmacodynamic properties of mAb that are dependent upon specific antigen binding may not be evident in animal studies conducted in species which do not express the antigen of interest. In some cases, xenograft models can be developed by introducing cells expressing the antigen of interest into immunodeficient mice (e.g. SCID or nude mice). Such models can provide information on specific targeting of desired cells, especially with radiolabeled mAb or immunoconjugates. Transgenic models expressing the antigen of interest are another possibility, if available. Whenever they are available, parallel models which explore the effects of mAb against the animal homolog of the antigen of interest can be informative. *In vivo* activity models have proven valuable in providing data which support a rationale for the proposed product use and in defining safety and toxicity. Animal disease models are available to study the effects of mAb on many inflammatory and autoimmune diseases, and allograft rejection. The extent of preclinical safety testing and the results of such testing will influence safety considerations for initial clinical trials (e.g. starting dose, dose escalation scheme, etc.).

b. Preclinical testing schemes should parallel to the greatest extent feasible those anticipated for clinical use with respect to dose, concentration, schedule, route, and duration. The range of doses selected for study should include at least one dose that is equivalent to and one dose that is a multiple of the highest anticipated clinical dose, with appropriate adjustments for interspecies differences in body size. A broad dose range should be explored. The highest doses tested should elicit adverse effects, whenever possible. Dose ranges are best established with a minimum of three doses. The linearity and overall shape of the dose response curve should also be defined by investigation of several doses and dosing intervals. If changes in manufacturing and/or formulation are made subsequent to conduct of preclinical studies, the decision to repeat some or all preclinical studies should depend on an assessment of the impact or likely impact of these changes on the product (see Section II.E.).

2. Animal toxicology studies

When planning toxicity testing for mAb, the following should be considered:

a. If the test article is an unconjugated antibody and there is no animal model of disease activity or animal that carries the relevant antigen, and cross-reactivity studies with human tissues are clearly negative, toxicity testing may not be necessary.

b. When a relevant animal model is available, an attempt should be made to study the dose-dependence of pharmacodynamic effects. The use of a broad range of doses, including high doses may allow a better prediction of the therapeutic index.

c. The properties of a relevant antigen in the animal should be comparable to those in humans in